



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2014

Novel, mercury-free synthetic pathway for trifluoromethylthio-substituted metallocenes

Hess, Jeannine ; Konatschnig, Sandro ; Morard, Sandra ; Pierroz, Vanessa ; Ferrari, Stefano ; Spingler, Bernhard ; Gasser, Gilles

Abstract: A novel synthetic pathway for trifluoromethylthioferrocene (3), which does not involve the use of toxic mercury(II)-based reagents, is described. The novel approach involves first the treatment of the commercially available bromoferrocene (1a) with NaSCN in the presence of copper(+I) to yield thiocyanatoferrocene (1), and then the reaction of 1 with the Rupper-Prakash reagent and tetrabutylammonium fluoride (TBAF) to give 3 in an overall yield of 60%. This approach could be extended for the preparation of thiocyanato-(4) and trifluoromethylthio-ruthenocene (7), which are herein both reported for the first time. Interestingly, diferrocenyl disulfide (2a) and diruthenocenyl disulfide (5) could be isolated as side-products during the synthesis of 3 and 7, respectively. All new compounds were unambiguously characterized by ¹H, ¹³C, and ¹⁹F NMR spectroscopy, mass spectrometry, cyclic voltammetry, elemental analysis, as well by X-ray crystallography for 1, 4, 4b, 5, 6, and 7. 1-7 were further tested for their toxic activity on cervical cancer (HeLa) and noncancerous (MRC-5) cell lines. All organometallic compounds were found either to be nontoxic or to have a moderate toxicity toward the cell lines used in this study.

DOI: <https://doi.org/10.1021/ic403169z>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-98808>

Journal Article

Accepted Version

Originally published at:

Hess, Jeannine; Konatschnig, Sandro; Morard, Sandra; Pierroz, Vanessa; Ferrari, Stefano; Spingler, Bernhard; Gasser, Gilles (2014). Novel, mercury-free synthetic pathway for trifluoromethylthio-substituted metallocenes. *Inorganic Chemistry*, 53(7):3662-3667.

DOI: <https://doi.org/10.1021/ic403169z>

A Novel, Mercury-Free Synthetic Pathway for Trifluoromethylthio-Substituted Metallocenes

Jeannine Hess,[†] Sandro Konatschnig,[†] Sandra Morard,[†] Vanessa Pierroz,^{†,‡} Stefano Ferrari,[‡] Bernhard Spingler,[†] and Gilles Gasser^{†,*}

[†] Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland.

[‡] Institute of Molecular Cancer Research, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland.

KEYWORDS. Ferrocene, Mercury-Free Synthesis, Metallocenes, Ruthenocene, Trifluoromethylthio Derivatives.

ABSTRACT: A novel synthetic pathway for trifluoromethylthioferrocene (**3**), which does not involve the use of toxic mercury(II)-based reagents, is described. The novel approach involves first the treatment of the commercially available bromoferrocene (**1a**) with NaSCN in the presence of copper(+I) to yield thiocyanatoferrocene (**1**), and then the reaction of **1** with the Ruppert-Prakash reagent and tetrabutylammonium fluoride (TBAF) to give **3** in an overall yield of 60%. This approach could be extended for the preparation of thiocyanato(**4**) and trifluoromethylthio-ruthenocene (**7**), which are herein both reported for the first time. Interestingly, diferrocenyl disulfide (**2a**) and diruthenocenyl disulfide (**5**) could be isolated as side-products during the synthesis of **3** and **7**, respectively. All new compounds were unambiguously characterized by ¹H, ¹³C and ¹⁹F NMR spectroscopy, mass spectrometry, cyclic voltammetry, elemental analysis as well by X-ray crystallography for **1**, **4**, **4b**, **5**, **6** and **7**. **1-7** were then tested for their toxic activity on a cervical cancer (HeLa) and on a non-cancerous (MRC-5) cell lines. All organometallic compounds were found to be either not toxic or to have a moderate toxicity towards the cell lines used in this study.

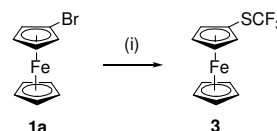
INTRODUCTION

Fluorinated compounds are playing a pivotal role in modern drug design. Several blockbuster drugs such as the anticancer drug 5-fluorouracil or the antidepressant drug Fluoxetine (Prozac®) bear one or several fluorine atom(s).¹⁻³ In fact, 20-25% of the drugs in the pharmaceutical pipeline contain a fluorine atom.³ This number is even more impressive if we take into account that organofluorine compounds are not present in natural products.³

Over the recent years, the trifluoromethylthio group (-SCF₃) has become a privileged pharmacophore in many agrochemical and pharmaceutical compounds notably due to its extremely high lipophilicity. The antiparasitic drug Toltrazuril and insecticide Fipronil are two successful examples of this class of compounds.⁴⁻⁷ Lipophilicity is often crucial for drug uptake and intracellular accumulation and can therefore decide on the bioactivity of a drug molecule.³ An impressive number of procedures and reagents have been recently reported to introduce an S-CF₃ group into various molecules.^{4,7-9} However, the currently available publications in this field are mainly focusing on purely organic compounds. The number of reports describing the preparation of S-CF₃-containing and more generally of fluorine-containing organometallic complexes is indeed relatively scarce.¹⁰⁻¹⁷ This is rather surprising since, over the recent years, organometallic compounds, and especially ferrocenyl derivatives,^{18,19} were shown to hold great promises as antimalarial,²⁰ antibacterial²¹ or anticancer²² agents.²³⁻²⁶ Of special synthetic interest is a recent article of Metzler-Nolte *et al.* describing the synthesis of trifluoromethylthioferrocene (**3**, Scheme 1).¹² In this work, the authors successfully prepared **3** in good yield starting from bromoferrocene (**1a**) by nucleophilic substitution of the bromo

group with SCF₃⁻ using Hg(SCF₃)₂ and copper bronze (Scheme 1).¹² Unfortunately, this procedure depends on a mercury(+II) based reagent, which is highly toxic and commercially available limited.²⁷ Taking into consideration the potential of fluorine-containing organometallic compounds, our group decided to explore an alternative approach, using less toxic reagents and mild conditions, to prepare not only **3** but also its heavier congener, trifluoromethylthioruthenocene (**7**). In this article, we describe the successful preparation of **3** and **7**. In addition, the toxic profile of all compounds synthesized in this work (**1-7**) on the cervical cancer (HeLa) and on the non-cancerous (MRC-5) cell lines is also reported. Furthermore, the electrochemical behavior of **1**, **1a**, **2a** and **3** is also described to evaluate the influence of the different electron-withdrawing substituent on the reduction potentials of the ferrocenyl moieties present in **1-3**.

Scheme 1. Synthetic Procedure for 3 described by Metzler-Nolte *et al.*¹²



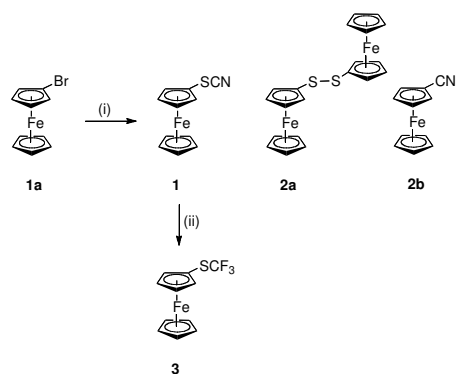
Conditions: (i) Hg(SCF₃)₂/Cu, hexane, reflux, overnight, 82%.

RESULTS AND DISCUSSION

Syntheses and characterization. The synthetic pathway used in our study to prepare **3** is outlined in Scheme 2. In a first

attempt, we aimed to synthesize **3** in a single reaction step by applying a modified procedure reported by Chen *et al.*,²⁸ namely by treatment of **1a** with S₈, copper(I) iodide and methyl fluorosulfonyldifluoroacetate in *N*-methylpyrrolidinone (NMP) at 100 °C overnight. These conditions only led to the formation of trace amounts of **3**. However, when the commercially available bromoferrocene (**1a**) was refluxed in the presence of sodium thiocyanate and catalytic amounts of Cu₂O, thiocyanatoruthenocene (**1**) could be obtained as an orange solid in 67% yield.^{29,30} In addition to the unreacted bromoferrocene, which could be recovered, the major side-product of this reaction is the literature-known diferrocenyl disulfide (**2a**). Cyanoferrocene (**2b**) could also be found in trace amounts as a minor side-product.³¹ The desired compound **3** was obtained by treating **1** with an excess of the commercially available Ruppert-Prakash reagent (Me₃SiCF₃) and a catalytic amount of a tetrabutylammonium fluoride solution in THF using slightly different conditions to those reported by Langlois *et al.*³²⁻³⁴ **3** was obtained as a yellow oil in excellent yield (90%) and the spectroscopic data matched those previously described by Metzler-Nolte *et al.*¹²

Scheme 2. Synthetic Pathway for 3

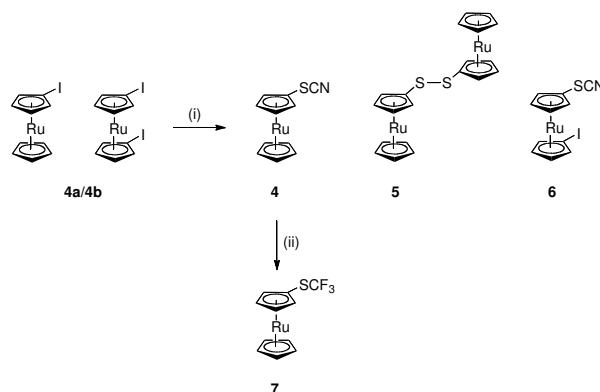


Conditions: (i) NaSCN, Cu₂O, dry MeCN, 64 h, reflux; 67%. (ii) Me₃SiCF₃, TBAF (THF soln. 1 M), dry THF, 10 min, -10 °C, 90%.

Encouraged by the promising results obtained for **3** and the importance of small functionalized metallocenes,³⁵ we decided to investigate the possibility to prepare ruthenocenyl analogues of **1** and **3**. Of note, ruthenocene derivatives were shown, over the last years, to have interesting biological properties and to be an interesting surrogate for ferrocenyl derivatives to understand the mechanism of action of these ferrocenyl compounds.³⁶⁻⁴⁰ The synthetic sequence to obtain the desired ruthenocene analogue trifluoromethylthioruthenocene (**7**) is outlined in Scheme 3. A mixture of mono- and diiodoruthenocene (**4a/4b**) was prepared according to a literature procedure and then refluxed in a similar fashion to **1a** with an excess of NaSCN and a catalytic amount of Cu₂O.⁴¹ Thiocyanatoruthenocene (**4**) was isolated as a colorless solid as the major product in 89% yield in addition to 1-1'-thiocyanatoiodoruthenocene (**6**) and diruthenocenyl disulfide (**5**) in 20% and 4% yields, respectively. The formation of **4**, **5** and **6** was confirmed by EI-MS with peaks at *m/z* = 288, 263 and 415 corresponding to [M⁺], [M-C₁₀H₉SRu]⁺ and [M⁺], respectively. Interestingly, the formation of a bis-substituted ruthenocenyl analogue, namely

dithiocyanatoruthenocene, was never observed during our trials to obtain **4**. In the last reaction step, **4** was reacted with an excess of the Ruppert-Prakash reagent and a catalytic amount of TBAF in THF at -10 °C to afford **7** in excellent yield (77%). The presence of **7** was ascertained by ¹H spectroscopy with the characteristic peak pattern at 4.85-4.84, 4.72-4.71 and 4.62 ppm, corresponding to the protons of the ruthenocenyl unit. Furthermore, only one single peak could be observed in ¹⁹F NMR spectroscopy at -46.3 ppm that can be attributed to the SCF₃ group.

Scheme 3. Synthetic Pathway for 7



Conditions: (i) NaSCN, Cu₂O, dry MeCN, 64 h, reflux; 89%. (ii) Me₃SiCF₃, TBAF (THF soln. 1 M), dry THF, 10 min, -10 °C, 77%.

X-ray crystallography. Single crystals of **1**, **4**, **4b**, **5**, **6** and **7** suitable for X-ray crystallography analysis could be grown by slow evaporation of the corresponding solutions of **1**, **4**, **4b**, **5**, **6** and **7** in chloroform. The ORTEP plots of **1** and **7** are shown in Figure 1 and those of **4**, **4b**, **5** and **6** in Figures S14 – S17 (see SI). All additional crystallographic information are presented in the SI. **1** crystallized in the orthorhombic space group Pnma and measurements indicate classical bond angles and distances for such types of bonds.⁴²⁻⁴⁴ **4** is essentially isostructural to **1** with the same space group Pnma and a slightly bigger cell. In both cases, the complexes display C_s symmetry that is shared with the mirror plane of the space group. **5** is not crystallizing in the same space group (P2₁) as the already published X-ray structure of **2a**.⁴⁵

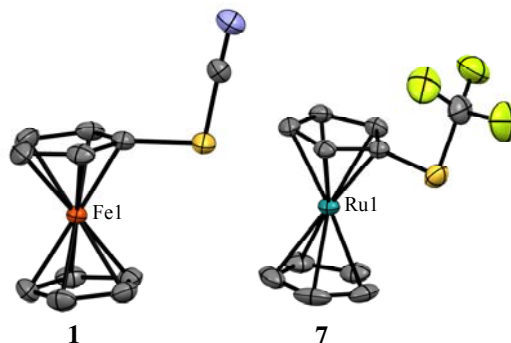


Figure 1. Molecular structure of **1** and **7** with atoms shown as thermal ellipsoids (drawn at 50% probability, hydrogen atoms are omitted for clarity).

Electrochemical studies. Voltammetric studies on compounds **1**, **1a**, **2a** and **3** at 1 mM concentrations in CH₃CN were carried out in order to investigate the influence of different substituted cyclopentadienyl rings on the oxidation/reduction of the ferrocene redox couple. For this purpose, a stationary glassy carbon (GC) electrode was used to perform the cyclic voltammetry with a scan rate of 100 mV·s⁻¹ in CH₃CN with tetrabutylammonium hexafluorophosphate (Bu₄NPF₆, 0.1 M) as the supporting electrolyte. A Pt electrode was used as the working electrode and Ag/AgCl as the reference electrode. As an internal reference, decamethylferrocene (DMFc, 0.25 mM) was used instead of the usual ferrocene in order to avoid overlaps of the studied compounds with the ferrocene oxidation process. The cyclic voltammogram of **1a**, **1**, **2a** and **3** are presented in the SI and the results are summarized in Table 1.

Table 1 – Cyclic Voltammetric Data for **1a**, **1**, **2a**, **3** in the presence of an internal reference (DMFc) at a GC Electrode in CH₃CN/Bu₄NPF₆ (0.1 M) with a scan rate of 100 mV·s⁻¹.

Compound	ΔE_p^0 vs DMFc ^{0/+} [mV]	ΔE_p [mV]
1a	+674	80
1	+802	89
2a	+615	90
	+779	79
3	+804	89

Oxidation peak potential = E_p^{ox} ; reduction peak potential = E_p^{red} ; formal redox potential $E_f^0 = (E_p^{ox} + E_p^{red})/2$.

All oxidation potentials are assigned to the reversible oxidation/reduction of the ferrocene redox couple and are in the expected range. **1a**, **1** and **3** show one reversible single oxidation wave, while **2a** has two reversible oxidation waves, one at +615 mV and the other at slightly higher potential +784 mV. The stronger electron withdrawing effect of the SCN- and SCF₃- group vs the Br- functionality is clearly visible in the higher oxidation potential of **1** and **3** (+802 mV and +804 mV) compared to **1a** (+674 mV).

Cytotoxicity studies. With the metallocene derivatives **1-7** in hand, we then investigated their toxicity towards the cervical cancer (HeLa) and the non-cancerous (MRC-5) cell lines. Cisplatin was used as reference compound. As can be seen in Table 2, the seven organometallic compounds showed either moderate cytotoxicity in the range of 29.0 - 61.2 μM or even no toxicity at all towards HeLa cells.

CONCLUSION

In summary, we present herein an efficient synthetic pathway for thiocyanato- and trifluoromethylthio- ferrocene and ruthenocene. Importantly, the synthetic route employed towards the trifluoromethylthio-metallocenes does not rely on a highly toxic and commercially available limited mercury(+II) salt. In addition, the crystallographic data of six organometallic compounds are reported. We could also demonstrate that all organometallic complexes prepared in this work had either modest or even no toxic activity on a cervical cancer (HeLa) and on a non-cancerous (MRC-5) cell line. We are confident that the synthetic conditions reported in this article will enable

the formation of higher substituted metallocenes with interesting biological properties.

Table 2 - Cytotoxicity activity (IC₅₀) of **1-7** against HeLa and MRC-5 cells.

Compound	IC ₅₀ values (μM)	
	HeLa	MRC-5
1a	> 100	> 100
1	38.5 ± 3.3	48.5 ± 1.0
2a	> 100	> 100
3	> 100	>100
4	61.2 ± 3.3	47.2 ± 7.5
5	38.7 ± 7.4	57.4 ± 10.9
6	29.0 ± 1.9	25.2 ± 4.1
7	> 100	> 100
Cisplatin	9.6 ± 1.2	17.6 ± 4.3

EXPERIMENTAL PART

Materials. All chemicals were of reagent grade quality or better, obtained from commercial suppliers and used without further purification. Solvents were used as received or distilled using standard procedures.⁴⁶ All preparations were carried out using standard Schlenk techniques and all reactions/compounds were protected from light as much as possible using aluminium foil. *Thin layer chromatography (TLC)* was performed using silica gel 60 F-254 (Merck) plates with detection of spots being achieved by exposure to UV light. *Column chromatography* was performed using Silica gel 60 (0.040-0.063 mm mesh, Merck). Eluent mixtures are expressed as volume to volume (v/v) ratios. Ruthenocene was synthesized according to a literature procedure.⁴⁷

Instrumentation and methods. ¹H, ¹³C and ¹⁹F NMR spectra were recorded in deuterated solvents on Bruker AV2-401, AV2-400, AV-500, AV-501 and DRX-500 spectrometers, at room temperature. The chemical shifts, δ, are reported in ppm (parts per million). The signals from the residual protons of deuterated solvent have been used as an internal reference.^{48,49} The abbreviations for the peak multiplicities are as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). *ESI mass spectrometry* was performed using a Bruker Esquire 6000 spectrometer. In the assignment of the mass spectra, the most intense peak is listed. *Cyclic voltammetric measurements* were performed at room temperature in acetonitrile solutions containing 0.1 M tetrabutyl ammonium hexafluorophosphate as the supporting electrolyte with a scan rate of 100 mV·s⁻¹ using a Methrom 757 VA Computrace electrochemical workstation. Solutions used in electrochemical measurements were deoxygenated by purging with nitrogen for at least 10 min before commencing the experiments. A conventional three electrode cell was employed which comprised a glassy carbon working electrode, a large surface area Pt counter electrode and an Ag/AgCl reference electrode. *EI-MS*: Mass spectrometry was performed on a Thermo DFS (ThermoFisher Scientific, Bremen, Germany) double-focusing magnetic sector mass spectrometer (geometry BE). Mass spectra were measured in electron impact (EI) mode at 70 eV, with solid probe inlet, source temperature of

200 °C, acceleration voltage of 5 kV, and resolution of 2'500. The instrument was scanned between m/z 30 and 900 at scan rate of 2 s / decade in the magnetic scan mode. Perfluorokerosene (PFK, Fluorochem, Derbyshire, UK) served for calibration. HR-EI-MS: High-resolution mass spectrometry was performed on a *Thermo DFS* (ThermoFisher Scientific, Bremen, Germany) double-focusing magnetic sector mass spectrometer (geometry BE). Mass spectra were measured in electron impact (EI) mode at 45 eV, with solid probe inlet, a source temperature of 200 °C, an acceleration voltage of 5 kV, and a resolution of 10'000. The instrument was scanned between e.g. m/z 300 und 350 at scan rate of 100-200 s / decade in the electric scan mode. Perfluorokerosene (PFK, Fluorochem, Derbyshire, UK) served for calibration. *Infrared spectra* were recorded on Perkin-Elmer FTIR spectrometer fitted with an ATR platform. Peak intensities are given as broad (b), very strong (vs), strong (s), medium (m) and weak (w).

Synthesis. Thiocyanatoferrocene (1) and diferrocenyl disulfide (2a). **1** was synthesized by refluxing bromoferrocene (**1a**, 500 mg, 1.90 mmol) in dry acetonitrile (65 mL), together with sodium thiocyanate (1.15 g, 14.22 mmol) in the presence of a catalytic amount of Cu_2O (0.07 g, 0.47 mmol) for 64 h. The reaction mixture was then allowed to reach room temperature, filtered and the solvent was removed *in vacuo*. The beige to orange crude solid was purified by column chromatography on silica using hexane:ethyl acetate (25:1) as eluent to give **1** (R_f = 0.35) as an orange solid and **2a** (R_f = 0.46) as bright orange crystals, respectively. Yields: **1**: 0.30 g (67%, 1.25 mmol); **2a**: 0.06 g (7.5%, 0.14 mmol). Spectroscopic data for **1** and **2a** matched those previously reported by Knox *et al.*³⁰ and Herberhold *et al.*,⁵⁰ respectively. To confirm the purity of **1** and **2a** for biological experiments, microanalysis and HR EI-MS were performed. Elemental Analysis for **1**: calcd. for $\text{C}_{11}\text{H}_9\text{FeNS}$: C, 54.35; H, 3.73; N, 5.76. Found = C, 54.39; H, 3.58; N, 5.10. HR EI-MS of **1**: calcd. for $\text{C}_{11}\text{H}_9\text{FeNS}$ (M^+) m/z (%) = 242.97996. Found m/z (%) = 242.97994. Elemental Analysis for **2a**: calcd. for $\text{C}_{20}\text{H}_{18}\text{Fe}_2\text{S}_2$: C, 55.30; H, 4.18. Found: C, 55.51; H, 4.12. HR EI-MS for **2a**: calcd. for $\text{C}_{20}\text{H}_{18}\text{Fe}_2\text{S}_2$ (M^+) m/z (%) = 433.95432. Found m/z (%) = 433.95484.

Trifluoromethylthioferrocene (3). **1** (0.05 g, 0.21 mmol) was dissolved in dry THF (50 mL), then degassed for 30 min and cooled to -10 °C. An excess of trifluoromethyltrimethylsilane (0.47 mL, 3.15 mmol) was then added to this yellow reaction solution. The temperature of the reaction mixture was maintained at -10 °C while a catalytic amount of tetrabutylammoniumfluoride solution (1 M in THF, 0.09 mL, 0.09 mmol) was added dropwise to the solution containing trifluoromethyltrimethylsilane and **1** over a period of 10 min. The reaction solution was further stirred for 5 min and then directly filtered through a silica plug. The product was further eluted from the plug by dichloromethane. Based on the observed volatility of **3** at low pressure and elevated temperature, the solution was dried by a gentle stream of N_2 gas to obtain the orange oily product **3**. Yield: 0.054 g (90%, 0.19 mmol). Spectroscopic data matched those previously reported by Metzler-Nolte *et al.*¹² To confirm the purity of **3** for the biological experiments, microanalysis and HR EI-MS were performed. Elemental Analysis for **3**: calcd. For $\text{C}_{11}\text{H}_9\text{F}_3\text{SFe}$: C, 46.18; H, 3.17. Found: C, 46.36; H, 3.34. HR EI-MS of **3**: calcd. for $\text{C}_{11}\text{H}_9\text{F}_3\text{FeS}$ (M^+) m/z (%) = 285.97210. Found m/z (%) = 285.97213.

Monoiodoruthenocene (4a) and Diiodoruthenocene (4b). The synthesis was carried out according to a modified literature procedure.⁴¹ Ruthenocene (0.565 g, 2.44 mmol) and KO^tBu (0.034 g, 0.303 mmol) were first dissolved in dry THF (40 mL) and the solution was cooled to -78 °C. To this solution was added a 1.9 M solution of $t\text{-BuLi}$ in pentane (2.6 mL, 4.94 mmol) over a period of 30 min while maintaining the temperature at -78 °C. After stirring for 30 min at -78 °C, a solution of I_2 (1.55 g, 6.11 mmol) in dry THF (20 mL) was added slowly to the reaction mixture at the same temperature. The reaction mixture was left to reach room temperature, further stirred for 24 h and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica, using hexane as eluent, to give **4a** (R_f = 0.44) and **4b** (R_f = 0.45) as light yellow solids. Yield: **4a**: 0.432 g (49%); **4b**: 0.188 g (16%). The characterization data for **4a** and **4b** matched those previously reported.⁴¹

Thiocyanatoruthenocene (4), diruthenocenyl disulfide (5) and 1-1'-thiocyanatoiodoruthenocene (6). **4** was synthesized according to the procedure described for **1**. A mixture of monoruthenocene (**4a**, 0.17 g, 0.47 mmol) and diiodoruthenocene (**4b**, 0.06 g, 0.12 mmol) was refluxed in dry acetonitrile (40 mL) with an excess of sodium thiocyanate (0.39 g, 4.83 mmol) and a catalytic amount of Cu_2O (0.01 g, 0.05 mmol) for 64 h. The reaction was then allowed to reach room temperature, filtered and evaporated *in vacuo*. The crude colorless solid was purified by column chromatography on silica using hexane:ethyl acetate (30:1) as eluent. **4** (R_f = 0.24, hexane:ethylacetate (25:1)) was obtained as colorless solid. Yield: 0.12 g (89%, 0.42 mmol). **5** (R_f = 0.36, hexane:ethylacetate (25:1)) and **6** (R_f = 0.15, hexane:ethylacetate (25:1)) could be also isolated as colorless solids. Yield **5**: 0.01 g (4%, 0.019 mmol). Yield **6**: 0.01 g (20%, 0.024 mmol).

Data for **4**: IR (Golden Gate, cm^{-1}): 3104, 2923, 2154, 1791, 1744, 1709, 1663, 1639, 1409, 1400, 1386, 1346, 1157, 1102, 1019, 1014, 999, 883, 843, 824, 812, 722. ^1H NMR (400 MHz, CDCl_3): δ/ppm = 4.92-4.91 (m, 2H, C_5H_4), 4.71-4.69 (m, 2H, C_5H_4), 4.65 (s, 5H, C_5H_5). ^{13}C NMR (125 MHz, CDCl_3): δ/ppm = 113.0, 75.9, 73.1, 72.8, 70.9. EI-MS: m/z (%) = 287.9 ($[\text{M}^+]$, 100), 262.9 ($[\text{M-CN}]^+$, 26), 198.9 ($[\text{M-C}_6\text{H}_4\text{N}]^+$, 13), 166.9 ($[\text{M-C}_6\text{H}_4\text{SN}]^+$, 24). HR EI-MS: calcd. for $\text{C}_{11}\text{H}_9\text{NRuS}$ (M^+) m/z (%) = 288.94937. Found m/z (%) = 288.94911. Elemental Analysis: calcd. for $\text{C}_{11}\text{H}_9\text{NRuS}$: C, 45.82; H, 3.15; N, 4.86. Found: C, 45.65; H, 3.07; N, 4.69.

Data for **5**: IR (Golden Gate, cm^{-1}): 3104, 2962, 2929, 1799, 1713, 1655, 1407, 1386, 1360, 1260, 1189, 1163, 1100, 1013, 996, 886, 802, 708. ^1H NMR (400 MHz, CDCl_3): δ/ppm = 4.75-4.74 (m, 4H, C_5H_4), 4.65-4.64 (m, 4H, C_5H_4), 4.56 (s, 10H, C_5H_5). ^{13}C NMR (125 MHz, CDCl_3): δ/ppm = 84.2, 76.3, 72.6, 72.0. EI-MS: m/z (%) = 263.0 ($[\text{M-C}_{10}\text{H}_9\text{SRu}]^+$, 100). HR EI-MS: calcd. for $\text{C}_{20}\text{H}_{18}\text{Ru}_2\text{S}_2$ (M^+) m/z (%) = 525.89419. Found m/z (%) = 525.89314. Elemental Analysis: calcd. for $\text{C}_{20}\text{H}_{18}\text{Ru}_2\text{S}_2$: C, 42.85; H, 3.96. Found: C, 43.30; H, 4.35.

Data for **6**: IR (Golden Gate, cm^{-1}): 3103, 2922, 2851, 2147, 1685, 1399, 1375, 1357, 1337, 1260, 1162, 1138, 1051, 1027, 1013, 1006, 915, 887, 866, 835, 820, 809, 727. ^1H NMR (400 MHz, CDCl_3): δ/ppm = 4.94-4.93 (m, 1H, C_5H_4), 4.92-4.91 (m, 1H, C_5H_4), 4.73-4.72 (m, 1H, C_5H_4), 4.57-4.56 (m, 1H, C_5H_4). ^{13}C NMR (125 MHz, CDCl_3): δ/ppm = 111.8, 79.8,

78.0, 75.5, 73.8, 72.1, 36.1. EI-MS: m/z (%) = 414.9 ($[M]^+$, 100), 288.0 ($[M-I]^+$, 78). HR EI-MS: calcd. for $C_{11}H_8NIRuS$ (M^+) m/z (%) = 414.84602. Found m/z (%) = 414.84617. Elemental Analysis: calcd. for $C_{11}H_8NIRuS$: C, 31.89; H, 1.95; N, 3.38. Found: C, 31.28; H, 1.92; N, 3.13.

Trifluoromethylthioruthenocene (7). **7** was synthesized using a similar procedure to the preparation of **3**. **4** (0.05 g, 0.17 mmol) was dissolved in dry THF (50 mL) which was previously degassed for 30 min. The colorless reaction solution was strongly stirred and cooled to $-10\text{ }^\circ\text{C}$. Trifluoromethyltrimethylsilane (0.37 mL, 2.55 mmol) was then added in excess to the reaction solution. A catalytic amount of tetrabutylammoniumfluoride solution (1 M in THF, 0.073 mL, 0.073 mmol) was added dropwise over a period of 10 min to the solution containing trifluoromethyltrimethylsilane and **4**. The temperature of the reaction was maintained at $-10\text{ }^\circ\text{C}$ while adding the tetrabutylammoniumfluoride solution. After further stirring for 5 min, the reaction was filtered through a silica plug. The product was further eluted with dichloromethane. Based on the observed volatility of **7** at low pressure and elevated temperature, the crude product was dried by a stream of N_2 gas and further purified by a column chromatography on silica using hexane as eluent. **7** (R_f = 0.56) was obtained as colorless solid. Yield: 0.042 g (77%, 0.13 mmol).

Data for **7**: IR (Golden Gate, cm^{-1}): 3087, 2924, 2851, 1671, 1411, 1390, 1167, 1109, 1023, 1013, 995, 892, 866, 839, 824, 809, 750, 723. ^1H NMR (400 MHz, CDCl_3): δ/ppm = 4.85–4.84 (m, 2H, C_5H_4), 4.72–4.71 (m, 2H, C_5H_4), 4.62 (s, 5H, C_5H_5). ^{13}C NMR (125 MHz, CDCl_3): δ/ppm = 132.5, 130.0, 127.5, 125.1, 77.8, 73.3, 72.3, 69.4. ^{19}F NMR (400 MHz, CDCl_3): δ/ppm = -46.3. EI-MS: m/z (%) = 332.0 ($[M]^+$, 36), 263.0 ($[M-\text{CF}_3]^+$, 100). HR EI-MS: calcd. for $C_{11}H_9F_3RuS$ (M^+) m/z (%) = 331.94151. Found m/z (%) = 331.94178. Elemental Analysis: calcd. for $C_{11}H_9F_3RuS$: C, 39.88; H, 2.74. Found: C, 40.01; H, 2.75.

Crystallographic studies. Crystallographic data were collected at 183(2) K on an Oxford Diffraction Xcalibur system with a Ruby detector using Mo K_α radiation ($\lambda = 0.7107\text{ \AA}$) that was graphite-monochromated. Suitable crystals were covered with oil (Infineum V8512, formerly known as Paratone N), placed on a nylon loop that is mounted in a Crystal-Cap MagneticTM from Hampton Research and immediately transferred to the diffractometer. The program suite CrysAlis-Pro[®] was used for data collection, multi-scan absorption correction and data reduction.⁵¹ The structures were solved with direct methods using SIR97⁵² and were refined by full-matrix least-squares methods on F^2 with SHELXL-97.⁵³ The structures were checked for higher symmetry with help of the program Platon.⁵⁴ Crystal **4b** contained 4 molecules in the asymmetric unit and was non-merohedrally twinned by a 180° rotation around the following vector in reciprocal space (hkl): 0 1 0. Both twin domains were integrated and merged into a hklf5 file. The twin ratio refined to 86.6 : 13.4. In the crystal structure of **5**, one non-substituted cp ring was found to be disordered in a 56:44 ratio.

Cell Culture. Human cervical carcinoma cells (HeLa) cells were cultured in DMEM (Gibco) supplemented with 5% fetal calf serum (FCS, Gibco), 100 U/ml penicillin, 100 $\mu\text{g}/\text{ml}$ streptomycin at $37\text{ }^\circ\text{C}$ and 5% CO_2 . The normal human fetal lung fibroblast MRC-5 cell line was maintained in F-10 medi-

um (Gibco) supplemented with 10% FCS (Gibco), penicillin (100 U/ml), and streptomycin (100 $\mu\text{g}/\text{ml}$).

Cytotoxicity Studies. Cytotoxicity studies were performed on two different cell lines, namely HeLa, and MRC-5, by a fluorometric cell viability assay using Resazurin (Promocell GmbH). Briefly, one day before treatment, cells were seeded in triplicates in 96-well plates at a density of 4×10^3 cells/well for HeLa and 7×10^3 for MRC-5 in 100 μl growth medium. Upon treating cells with increasing concentrations of Fc-PZQ derivatives for 48h, the medium was removed, and 100 μl complete medium containing Resazurin (0.2 mg/ml final concentration) were added. After 4h of incubation at $37\text{ }^\circ\text{C}$, fluorescence of the highly red fluorescent product Resorufin was quantified at 590 nm emission with 540 nm excitation wavelength in a SpectraMax M5 microplate Reader.

AUTHOR INFORMATION

Supporting Information

^1H , ^{13}C and ^{19}F NMR spectra (Figures S1-9), Cyclic voltammograms (Figures S10-12) and crystallographic data (Table S1 and Figures S13-16). This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*G.G.: e-mail, gilles.gasser@chem.uzh.ch; fax, +41 44 635 6803; tel, + 41 44 635 4630 ; web, www.gassergroup.com

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was the Swiss National Science Foundation (Professorship N° PP00P2_133568 to G.G), the University of Zurich (G.G and S.F.), the Stiftung für Wissenschaftliche Forschung of the University of Zurich (G.G. and S.F.), the Stiftung zur Krebsbekämpfung (S.F), the Huggenberger-Bischoff Stiftung (S.F) and the University of Zurich Priority Program (S.F.). We thank Dr. Max Lieb for helpful discussions.

REFERENCES

- (1) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27-33.
- (2) Shah, P.; Westwell, A. D. *J. Enz. Inhib. Med. Chem.* **2007**, *22*, 527-540.
- (3) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330.
- (4) Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K.-W. *Angew. Chem. Int. Ed.* **2013**, *52*, 1548-1552.
- (5) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; John Wiley and Sons: New York, 1979.
- (6) Boiko, V. N. *Beilstein J. Org. Chem.* **2010**, *6*, 880-921.
- (7) Zhang, C.-P.; Vacic, D. A. *J. Am. Chem. Soc.* **2011**, *134*, 183-185.
- (8) Tlili, A.; Billard, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 6818-6819.
- (9) Chen, C.; Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 12454-12457.
- (10) Popov, V. I.; Lib, M.; Haas, A. *Ukr. Khim. Zh. (Russ. Ed.)* **1990**, *56*, 1115-16.

- (11) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160-171, and references therein.
- (12) Rhode, C.; Lemke, J.; Lieb, M.; Metzler-Nolte, N. *Synthesis* **2009**, 2009, 2015-2018.
- (13) Maschke, M.; Lieb, M.; Metzler-Nolte, N. *Eur. J. Inorg. Chem.* **2012**, 2012, 5953-5959.
- (14) Miyaji, H.; Kim, D.-S.; Chang, B.-Y.; Park, S.-M.; Ahn, K. H. *Bull. Korean Chem. Soc.* **2008**, *29*, 2355-2360.
- (15) Song, Q.-b.; Lin, R.-x.; Teng, M.-y.; Zhang, J.; Ma, C.-a. *Synthesis* **2006**, 123-127.
- (16) Hedberg, F. L.; Rosenberg, H. *J. Organomet. Chem.* **1971**, *28*, C14-C16.
- (17) Akiyama, T.; Kato, K.; Kajitani, M.; Sakaguchi, Y.; Nakamura, J.; Hayashi, H.; Sugimori, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3531-3537.
- (18) Metzler-Nolte, N.; Salmann, M. In *Ferrocenes: Ligands, Materials and Biomolecules*; Stepnicka, P., Ed.; John Wiley & Sons Ltd.: Chichester, UK 2008, p 499-639.
- (19) van Staveren, D. R.; Metzler-Nolte, N. *Chem. Rev.* **2004**, *104*, 5931-5985, and references therein.
- (20) Biot, C.; Dive, D. In *Medicinal Organometallic Chemistry*; Jaouen, G., Metzler-Nolte, N., Eds.; Springer-Verlag: Heidelberg, 2010; Vol. 32, p 155-193.
- (21) Patra, M.; Gasser, G.; Metzler-Nolte, N. *Dalton Trans.* **2012**, *41*, 6350-6358.
- (22) Gasser, G.; Ott, I.; Metzler-Nolte, N. *J. Med. Chem.* **2011**, *54*, 3-25.
- (23) Jaouen, G. *Bioorganometallics: Biomolecules, Labelling, Medicine*; Wiley-VCH Verlag GmbH, Weinheim, 2006.
- (24) Bruijninx, P. C. A.; Sadler, P. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 197-206, and references therein.
- (25) Gasser, G.; Metzler-Nolte, N. *Curr. Opin. Chem. Biol.* **2012**, *16*, 84-91.
- (26) Hartinger, C. G.; Dyson, P. J. *Chem. Soc. Rev.* **2009**, *38*, 391-401.
- (27) Tyrra, W.; Naumann, D.; Hoge, B.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2003**, *119*, 101-107.
- (28) Chen, Q.-Y.; Duan, J.-X. *J. Chem. Soc., Chem. Commun.* **1993**, 918-919.
- (29) Nefedov, V. A.; Nefedova, M. N. *Zh. Obshch. Khim.* **1966**, *36*, 122-126.
- (30) Knox, G. R.; Pauson, P. L.; Willison, D.; Solcaniova, E.; Toma, S. *Organometallics* **1990**, *9*, 301-306.
- (31) Kinuta, H.; Kita, Y.; Rémond, E.; Tobisu, M.; Chatani, N. *Synthesis* **2012**, *44*, 2999-3002.
- (32) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195-2198.
- (33) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393-395.
- (34) Billard, T.; Large, S.; Langlois, B. R. *Tetrahedron Lett.* **1997**, *38*, 65-68.
- (35) Leonidova, A.; Joshi, T.; Nipkow, D.; Frei, A.; Penner, J.-E.; Konatschnig, S.; Patra, M.; Gasser, G. *Organometallics* **2013**, *32*, 2037-2040.
- (36) Beagley, P.; Blackie, M. A. L.; Chibale, K.; Clarkson, C.; Moss, J. R.; Smith, P. J. *J. Chem. Soc., Dalton Trans.* **2002**, 4426-4433.
- (37) Dubar, F.; Egan, T. J.; Pradines, B.; Kuter, D.; Ncokazi, K. K.; Forge, D.; Paul, J.-F. o.; Pierrot, C.; Kalamou, H.; Khalife, J.; Buisine, E.; Rogier, C.; Vezin, H.; Forfar, I.; Slomianny, C.; Trivelli, X.; Kapisnikov, S.; Leiserowitz, L.; Dive, D.; Biot, C. *ACS Chem. Biol.* **2012**, *6*, 275-287.
- (38) Pigeon, P.; Top, S.; Vessières, A.; Huché, M.; Hillard, E. A.; Salomon, E.; Jaouen, G. *J. Med. Chem.* **2005**, *48*, 2814-2821.
- (39) Zagermann, J.; Klein, K.; Merz, K.; Molon, M.; Metzler-Nolte, N. *Eur. J. Inorg. Chem.* **2011**, 2011, 4212-4219.
- (40) Gross, A.; Neukamm, M.; Metzler-Nolte, N. *Dalton Trans.* **2011**, *40*, 1382-1386.
- (41) Bednarik, L.; Neuse, E. *J. Organomet. Chem.* **1979**, *168*, C8-C12.
- (42) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2*, **1987**, S1-19.
- (43) Gasser, G.; Carr, J. D.; Coles, S. J.; Hursthouse, M. B.; Cafferkey, S. M.; Stoeckli-Evans, H.; Tucker, J. H. R. *J. Organomet. Chem.* **2010**, *695*, 249-255.
- (44) Gasser, G.; Fischmann, A. J.; Forsyth, C. M.; Spiccia, L. *J. Organomet. Chem.* **2007**, *692*, 3835-3840.
- (45) Hartmann, S.; Winter, R. F.; Scheiring, T.; Wanner, M. *J. Organomet. Chem.* **2001**, 637-639 240-250.
- (46) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; 4th Edition ed.; Butterworth-Heinemann: Oxford (UK), 1996.
- (47) Sagae, T.; Google Patents: 2006, WO/2004/013150 A1.
- (48) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.
- (49) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176-2179.
- (50) Herberhold, M.; Leitner, P. *J. Organomet. Chem.* **1987**, *336*, 153-161.
- (51) *Xcalibur CCD system*; 171.32 ed.; Oxford Diffraction Ltd: Oxford, UK, 2007.
- (52) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115-119.
- (53) Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112-122.
- (54) Spek, A. L. *J. Appl. Cryst.*, **2003**, *36*, 7-13.

For Table of Contents Only

Trifluoromethylthioferrocene and its higher homologue trifluoromethylthioruthenocene, which is reported for the first time, were prepared in a reaction sequence involving first the treatment of the respective halogeno-metallocenes with NaSCN in the presence

of copper(+I) to yield the thiocyanato-metallocenes and then the reaction of the latter with the Rupper-Prakash reagent and tetrabutylammonium fluoride to give the expected organometallic compounds in good yields. Importantly, this synthetic procedure does not involve the use of mercury reagents.

